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Uptodate Review of Restless Legs Syndrome - Mechanism, Clinical Impacts and Management

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Restless legs syndrome (RLS) is a common movement disorder of wake and sleep. RLS diagnosis is based on clinical assessment. The key diagnostic feature is an irresistible urge to move the legs, usually—but not always—in response to an unpleasant sensation. Unpleasant sensations without the urge to move are not sufficient for diagnosis. In 1995, the International Restless Legs Study Group (IRLSSG) first proposed a set of formal clinical criteria which were revised in 2014. ICSD-3 or DSM-5 diagnosis criteria are available. Although the pathophysiology still remains somewhat uncertain, RLS is considered a complex condition including genetic background. Numerous studies suggested that brain iron deficiency is key pathophysiology of RLS, which is supported by genetic studies. The involvement of the dopaminergic system in pathophysiology of RLS is supported by the therapeutic benefit of dopamine agonists. Some studies have supported a role for altered glutamatergic neurotransmission in RLS. Also, some studies iron deficiency might lead to hypersensitivity off the glutamatergic cortico-striatal terminals in rodents. Brain iron deficiency produced a significant changes of adenosine receptors. A better understanding of the pathophysiology will ultimately assist in the detection and development of new treatments that will specifically target the disease.

Notably, RLS prevalence in hemodialysis (HD) patients is much higher than in the general population reaching approximately 30%. Severe RSL symptoms were associated with substantially diminished physical functioning and mental well-being. Some studies suggested that severe restless legs symptoms were independently associated with an increased risk for death after controlling for comorbidity, demographic variables, and potential clinical confounders. However, these findings are not consistent. Further studies should reveal the clinical outcome of RLS in HD patients. Pharmacological treatment including α2δ ligands(gabapentin), dopaminergic agents, iron supplement and opioids, needs to be instituted when the symptoms are clinically significant, when they occur with frequency and severity affecting quality of life. Levodopa is considered efficacious but conveys a high risk of augmentation. All patients on dopamine agonists should be monitored for augmentation and impulse control disorders.

Recently, the greatest change to the prior practice guidelines was the encouragement to use α2δ ligands as first-line treatment rather than dopamine receptor agonists. Current guidelines recommend starting with monotherapy; combination therapy has been anecdotally effective but randomized clinical trial data are lacking. Non-pharmacologic treatments have been studied. Single studies have reported symptom improvement with caffeine, alcohol, massage, hot baths, yoga, nerve stimulation or spinal current stimulation, but the evidence is lack. Further clinical trials are needed to better evaluate the risk to benefit of treating RLS associated with HD patients.